NDA 19-002/S-009 JUL 12 2000

The R.W. Johnson Pharmaceutical Research Institute
Attention: Mr. William Sisco
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Sisco:

Please refer to your supplemental new drug application dated March 8, 1999, received March 11, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vascor (bepridil) Tablets.

We acknowledge receipt of your submission dated June 14, 2000 that constituted a complete response to our February 2, 2000 action letter.

This supplemental new drug application provides for final printed labeling revised as follows:

The following paragraph was added to **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism** subsection:

> Bepridil is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug is greater in patients with impaired renal function. Peak plasma concentration of bepridil was increased 3-fold and $t_{1/2}$ was increased more than 2-fold in elderly (>74 years) receiving oral bepridil 100 mg twice daily for 3 weeks compared to younger volunteers (see **PRECAUTIONS-Geriatric Use).**

The **PRECAUTIONS** section was revised to include a **Geriatric** Use subsection:

> **Geriatric** Use: Clinical studies of bepridil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Bepridil is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug is greater in patients with impaired renal function (see **CLINICAL PHARMACOLOGY-Pharmacokinetics and Metabolism).**

In addition, the unit dose of 100s was deleted from the **HOW SUPPLIED** section, and the Manufacturing Statement was changed from:

McNeil Pharmaceutical
McNeilab, Inc.
Spring House, PA 19477

to:

OMP Division
Ortho-McNeil Pharmaceutical, Inc.
Raritan, NJ 08869

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted June 14, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 3l4.80 and 314.81.

If you have any questions, please call:

Mr. David Roeder
Regulatory Project Manager
(301) 594-5332

Sincerely,

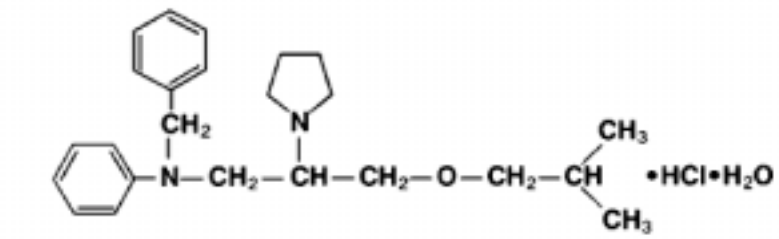
Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

VASCOR®
(bepridil hydrochloride)
Tablets
For Oral Administration

DESCRIPTION

VASCOR (bepridil hydrochloride) is a calcium channel blocker that has well characterized anti-anginal properties and known but poorly characterized type 1 anti-arrhythmic and antihypertensive properties. It has inhibitory effects on both the slow calcium and fast sodium inward currents in myocardial and vascular smooth muscle, interferes with calcium binding to calmodulin, and blocks both voltage and receptor operated calcium channels. It is not related chemically to other calcium channel blockers such as diltiazem hydrochloride, nifedipine, and verapamil hydrochloride.

Bepridil hydrochloride monohydrate is a white to off-white, crystalline powder with a bitter taste. It is slightly soluble in water, very soluble in ethanol, methanol and chloroform, and freely soluble in acetone. The molecular weight of bepridil hydrochloride monohydrate is 421.02. Its molecular formula is $C_{24}H_{34}N_2O \bullet HCl \bullet H_2O$. The structural formula is:



(±)-ß-[(2-Methylpropoxy)methyl] -*N*-phenyl-*N*-(phenylmethyl)-l-pyrrolidineethanamine monohydrochloride monohydrate

VASCOR is available as film-coated tablets for oral use containing 200, 300, or 400 mg of bepridil hydrochloride monohydrate. Inactive ingredients: hydroxypropyl methyl-cellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, pregelatinized corn starch, corn starch, titanium dioxide, FD&C Blue #1.

CLINICAL PHARMACOLOGY

VASCOR (bepridil hydrochloride) inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. This has been demonstrated in isolated myocardial and vascular smooth muscle preparations in which both the slope of the calcium dose response curve and the maximum calcium-induced inotropic response were significantly reduced by bepridil hydrochloride. In cardiac myocytes *in vitro*, bepridil hydrochloride was shown to be tightly bound to actin. A negative inotropic effect can be seen in the isolated guinea pig atria.

In *in vitro* studies, bepridil hydrochloride has also been demonstrated to inhibit the sodium inward current. Reductions in the maximal upstroke velocity and the amplitude of the action potential, as well as increases in the duration of the normal action potential, have been observed. Additionally, bepridil hydrochloride has been shown to possess local anesthetic activity in isolated myocardial preparations. It effects electrophysiological changes that are observed with several classes of anti-arrhythmic agents.

Clinical Studies

In controlled clinical studies with 200-400 mg of VASCOR, given as a once daily dose, exercise tolerance was improved and angina frequency and daily nitroglycerin use was reduced compared to placebo. Improvement in exercise performance was dose related. In one controlled clinical study, VASCOR was added to propranolol in daily doses of up to 240 mg. The 200-400 mg dose of VASCOR was well tolerated [patients entered were not allowed to be in NYHA Class III or IV heart failure] and there was an added effect of VASCOR on exercise tolerance.

In another controlled clinical study, VASCOR in doses of up to 400 mg/day, significantly improved exercise tolerance compared to diltiazem hydrochloride in patients refractory to diltiazem hydrochloride therapy.

Mechanism of Action: The precise mechanism of action for VASCOR as an anti-anginal agent remains to be fully determined, but is believed to include the following mechanisms:

VASCOR regularly reduces heart rate and arterial pressure at rest and at a given level of exercise by

dilating peripheral arterioles and reducing total peripheral resistance (afterload) against which the heart works. In exercise tolerance tests in patients with stable angina the heart rate/blood pressure product was reduced with VASCOR for a given work load.

Hemodynamic Effects: VASCOR produces dose dependent slowing of the heart, and reflex tachycardia is not seen. The mean decrease in heart rate in US clinical trials was 3 b.p.m. Orally administered VASCOR also produces modest decreases (less than 5 mm Hg) in systolic and diastolic blood pressure in normotensive patients and somewhat larger decreases in hypertensive patients. Intravenous administration of VASCOR is associated with a modest reduction in left ventricular contractility (dP/dt), and increased filling pressure, but radionuclide cineangiography studies in angina patients demonstrated improvement in ejection fraction at rest and during exercise following oral VASCOR therapy. Patients with impaired cardiac function [overt heart failure] were not included in these studies.

Electrophysiological Effects: Intravenous administration of VASCOR in man prolongs the effective refractory periods of the atria and ventricles, and the functional refractory period of the AV node. There was a tendency for the AV node effective refractory period and A-H interval to be increased as well. Intravenous and oral administration of VASCOR slow heart rate, prolong the QT and QTc intervals, and alter the morphology of the T-wave (indentation). In clinical trials with angina patients, the mean percent prolongation of the QTc interval was approximately 8%, and of QT about 10%. The prolongation of QT is dose related, varying from about 0.030 sec at doses of 200 mg once a day to 0.055 sec at 400 mg once a day. Upon cessation of therapy, the ECG gradually normalizes. No instances of greater than first-degree heart block have been observed in US controlled or open clinical studies with VASCOR, and first-degree heart block occurred in 0.2% of patients in these studies.

Pulmonary Function: In healthy subjects and asthmatic patients, intravenous VASCOR did not cause bronchoconstriction. VASCOR has been safely used in asthmatic patients and in patients with chronic obstructive lung disease.

Pharmacokinetics and Metabolism: In studies with healthy volunteers, VASCOR is rapidly and completely absorbed after oral administration. The time to peak bepridil plasma concentration is about 2 to 3 hours. Over a ten day period, approximately 70% of a single dose of VASCOR is excreted in the urine and 22% in the feces, as metabolites of bepridil. Excretion of unmetabolized drug is negligible. In healthy male volunteers, the relationship between dose and steady-state blood levels of bepridil was linear over the range of 200 to 400 mg/day. Elimination of bepridil is biphasic, with a distribution half-life of about 2 hours. The terminal elimination half-life following the cessation of multiple dosing averaged 42 hours (range 26-64 hours). However, during a given dosing interval, decay from the peak concentration occurs relatively rapidly indicating a dosing interval half-life shorter than 24 hours. Following once-daily dosing with therapeutic doses, steady-state was reached in about 8 days in healthy volunteers. The clearance of bepridil decreases after multiple dosing.

Clearance of bepridil in angina patients was lower than that in healthy volunteers, resulting in higher average plasma bepridil concentrations. At steady state, maximum bepridil concentrations averaged 2332 ng/ml (range 1451 to 3609) and mean minimum concentrations were 1174 ng/ml (range 226 to 2639) in angina patients following 300 mg/day doses of VASCOR.

Bepridil is more than 99% bound to plasma proteins. Administration of VASCOR after a meal resulted in a clinically insignificant delay in time to peak concentration, but neither peak bepridil plasma levels nor the extent of absorption was changed.

Bepridil is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug is greater in patients with impaired renal function. Peak plasma concentration of bepridil was increased 3-fold and $t_{1/2}$ was increased more than 2-fold in elderly (>74 years) receiving oral bepridil 100 mg twice daily for 3 weeks compared to younger volunteers (see **PRECAUTIONS-Geriatric Use).**

Bepridil passes through the placental barrier. Bepridil may cause uterine hypotonia.

INDICATIONS AND USAGE

Chronic Stable Angina (Classic Effort-Associated Angina)

VASCOR (bepridil hydrochloride) is indicated for the treatment of chronic stable angina (classic effort-associated angina). Because VASCOR has caused serious ventricular arrhythmias, including torsades de pointes type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to, or are intolerant of, other anti-anginal medication.

VASCOR may be used alone or in combination with beta blockers and/or nitrates. Controlled clinical studies have shown an added effect when VASCOR is administered to patients already receiving propranolol.

CONTRAINDICATIONS

VASCOR (bepridil hydrochloride) is contraindicated in patients with a known sensitivity to bepridil hydrochloride.

VASCOR is contraindicated in (1) patients with a history of serious ventricular arrhythmias (see WARNINGS Induction of New Serious Arrhythmias), (2) patients with sick sinus syndrome or patients with second- or third-degree AV block, except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients with uncompensated cardiac insufficiency, (5) patients with congenital QT interval prolongation (see WARNINGS), and (6) patients taking other drugs that prolong QT interval (see PRECAUTIONS - Drug Interactions).

WARNINGS

Induction of New Serious Arrhythmias

VASCOR (bepridil hydrochloride) has Class 1 anti-arrhythmic properties and, like other such drugs, can induce new arrhythmias, including VT/VF. In addition, because of its ability to prolong the QT interval, VASCOR can cause torsades de pointes type ventricular tachycardia. Because of these properties VASCOR should be reserved for patients in whom other anti-anginal agents do not offer a satisfactory effect.

In US clinical trials, the QT and QTc intervals were commonly prolonged by VASCOR in a dose-related fashion. The mean prolongation of QTc was 8% and of QT was 10%. Increases of 25% or more were not uncommon, occurring in 5% of the studied population for QTc and 8.7% of the studied population for QT. Increased QT and QTc may be associated with torsades de pointes type VT, which was seen at least briefly, in about 1.0% of patients in US trials; in many cases, however, patients with marked prolongation of QTc were taken off VASCOR therapy. All of the US patients with torsades de pointes had a prolonged QT interval and relatively low serum potassium. French marketing experience has reported over one hundred verified cases of torsades de pointes. While this number, based on total use, represents a rate of only 0.01%, the true rate is undoubtedly much higher, as spontaneous reporting systems all suffer from substantial under reporting.

Torsades de pointes is a polymorphic ventricular tachycardia often but not always associated with a prolonged QT interval, and often drug induced. The relation between the degree of QT prolongation and the development of torsades de pointes is not linear and the likelihood of torsades appears to be increased by hypokalemia, use of potassium wasting diuretics, and the presence of antecedent bradycardia. While the safe upper limit of QT is not defined, it is suggested that the interval not be permitted to exceed 0.52 seconds during treatment. If dose reduction does not eliminate the excessive prolongation, VASCOR should be stopped.

Because most domestic and foreign cases of torsades have developed in patients with hypokalemia, usually related to diuretic use or significant liver disease, if concomitant diuretics are needed, low doses and addition or primary use of a potassium sparing diuretic should be considered and serum potassium should be monitored.

VASCOR has been associated with the usual range of pro-arrhythmic effects characteristic of Class 1 anti-arrhythmics (increased premature ventricular contraction rates, new sustained VT, and VT/VF that is more resistant to sinus rhythm conversion). Use in patients with severe arrhythmias (who are most susceptible to certain pro-arrhythmic effects) has been limited, so that risk in these patients is not defined.

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic nonlife-threatening ventricular arrhythmias who had myocardial infarctions more than six days but less than two years previously, an excess mortality/non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The applicability of these results to other populations (e.g., those without recent myocardial infarction) or to other anti-arrhythmic drugs is uncertain, but at present it is prudent to consider any drug documented to provoke new serious arrhythmias or worsening of preexisting arrhythmias as having a similar risk and to avoid their use in the post-infarction period.

Agranulocytosis: In US clinical trials of over 800 patients treated with VASCOR for up to five years, two cases of marked leukopenia and neutropenia were reported. Both patients were diabetic and elderly. One died with overwhelming gram-negative sepsis, itself a possible cause of marked leukopenia. The other patient recovered rapidly when VASCOR was stopped.

Congestive Heart Failure: Congestive heart failure has been observed infrequently (about l%) during US controlled clinical trials, but experience with the use of VASCOR in patients with significantly impaired ventricular function is limited. There is little information on the effect of concomitant adminis-

tration of VASCOR and digoxin; therefore, caution should be exercised in treating patients with congestive heart failure.

Hepatic Enzyme Elevation: In US clinical studies with VASCOR in about 1000 patients and subjects, clinically significant (at least 2 times the upper limit of normal) transaminase elevations were observed in approximately 1% of the patients. None of these patients became clinically symptomatic or jaundiced and values returned to normal when the drug was stopped.

Hypokalemia: In clinical trials VASCOR has not been reported to reduce serum potassium levels. Because hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency should be corrected before VASCOR therapy is initiated and normal potassium concentrations should be maintained during VASCOR therapy. Serum potassium should be monitored periodically.

PRECAUTIONS

General

Caution should be exercised when using VASCOR (bepridil hydrochloride) in patients with left bundle branch block or sinus bradycardia (less than 50 b.p.m.). Care should also be exercised in patients with serious hepatic or renal disorders because such patients have not been studied and bepridil is highly metabolized, with metabolites excreted primarily in the urine.

Recent Myocardial Infarction

In US clinical trials with VASCOR, patients with myocardial infarctions within three months prior to initiation of drug treatment were excluded. The initiation of VASCOR therapy in such patients, therefore, cannot be recommended.

Pulmonary Infiltration

There have been cases of noninfective, noncardiogenic pulmonary interstitial infiltrates (with or without the presence of eosinophilia), including cases of pulmonary fibrosis, in patients taking VASCOR. These cases may present as dyspnea or cough within a few weeks of commencing VASCOR ; infiltrates may be seen on chest x-ray.

Although the relationship of pulmonary infiltration to VASCOR is unclear, any patient who develops dyspnea or cough of unspecified etiology should be adequately evaluated. If other causes cannot be identified, discontinuation of VASCOR therapy should be considered.

Information for Patients

Since QT prolongation is not associated with defined symptomatology, patients should be instructed on the importance of maintaining any potassium supplementation or potassium sparing diuretic, and the need for routine electrocardiograms and periodic monitoring of serum potassium.

The following Patient Information is printed on the carton label of each unit of use bottle of 30 tablets:

> As with any medication you take, you should notify your physician of any changes in your overall condition. Be sure to follow your physician's instructions regarding follow-up visits. Please notify any physician who treats you for a medical condition that you are taking VASCOR® (bepridil hydrochloride), as well as any other medications.

Drug Interactions

Nitrates: The concomitant use of VASCOR with long- and short-acting nitrates has been safely tolerated in patients with stable angina pectoris. Sublingual nitroglycerin may be taken if necessary for the control of acute angina attacks during VASCOR therapy.

Beta-blocking Agents: The concomitant use of VASCOR and beta-blocking agents has been well tolerated in patients with stable angina. Available data are not sufficient, however, to predict the effects of concomitant medication on patients with impaired ventricular function or cardiac conduction abnormalities (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Digoxin: In controlled studies in healthy volunteers, bepridil hydrochloride either had no effect (one study) or was associated with modest increases, about 30% (two studies) in steady-state serum digoxin concentrations. Limited clinical data in angina patients receiving concomitant bepridil hydrochloride and digoxin therapy indicate no discernible changes in serum digoxin levels. Available data are neither sufficient to rule out possible increases in serum digoxin with concomitant treatment in some patients, nor other possible interactions, particularly in patients with cardiac conduction abnormalities (Also see WARNINGS-Congestive Heart Failure).

Oral Hypoglycemics: VASCOR has been safely used in diabetic patients without significantly lowering their blood glucose levels or altering their need for insulin or oral hypoglycemic agents.

General Interactions: Certain drugs could increase the likelihood of potentially serious adverse effects with bepridil hydrochloride. In general, these are drugs that have one or more pharmacologic activities similar to bepridil hydrochloride, including anti-arrhythmic agents such as quinidine and procainamide, cardiac glycosides and tricyclic anti-depressants. Anti-arrhythmics and tricyclic anti-depressants could exaggerate the prolongation of the QT interval observed with bepridil hydrochloride. Cardiac glycosides could exaggerate the depression of AV nodal conduction observed with

bepridil hydrochloride.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenicity was revealed in one lifetime study in mice at dosages up to 60 times (for a 60 kg subject) the maximum recommended dosage in man. Unilateral follicular adenomas of the thyroid were observed in a study in rats following lifetime administration of high doses of bepridil hydrochloride, i.e., ???100 mg/kg/day (20 times the usual recommended dose in man). No mutagenic or other genotoxic potential of bepridil hydrochloride was found in the following standard laboratory tests: the Micronucleus Test for Chromosomal Effects, the Liver Microsome Activated Bacterial Assay for Mutagenicity, the Chinese Hamster Ovary Cell Assay for Mutagenicity, and the Sister Chromatid Exchange Assay. No intrinsic effect on fertility by bepridil hydrochloride was demonstrated in rats. In monkeys, at 200 mg/kg/day, there was a decrease in testicular weight and spermatogenesis. There were no systematic studies in man related to this point. In rats, at doses up to 300 mg/kg/day, there was no observed alteration of mating behavior nor of reproductive performance.

Usage in Pregnancy
Pregnancy Category C. Reproductive studies (fertility and peri-postnatal) have been conducted in rats. Reduced litter size at birth and decreased pup survival during lactation were observed at maternal dosages 37 times (on a mg/kg basis) the maximum daily recommended therapeutic dosage. In teratology studies, no effects were observed in rats or rabbits at these same dosages. There are no well-controlled studies in pregnant women. Use VASCOR in pregnant or nursing women only if the potential benefit justifies the potential risk.

Nursing Mothers
Bepridil is excreted in human milk. Bepridil concentration in human milk is estimated to reach about one third the concentration in serum. Because of the potential for serious adverse reactions in nursing infants from VASCOR a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of VASCOR in children have not been established.

Geriatric Use: Clinical studies of bepridil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Bepridil is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug is greater in patients with impaired renal function (see **CLINICAL PHARMACOLOGY-Pharmacokinetics and Metabolism).**

ADVERSE REACTIONS
Adverse reactions were assessed in placebo and active-drug controlled trials of 4-12 weeks duration and longer-term uncontrolled studies. The most common side effects occurring more frequently than in control groups were upper gastrointestinal complaints (nausea, dyspepsia or GI distress) in about 22%, diarrhea in about 8%, dizziness in about l5%, asthenia in about 10% and nervousness in about 7%. The adverse reactions seen in at least 2% of bepridil patients in controlled trials are shown in the following table.

Adverse Experiences by Body System and Treatment in Greater Than 2% of Bepridil Patients in Controlled Trials

Adverse Reaction	Bepridil HCl (N = 529)	Nifedipine (N = 50)	Propranolol (N = 88)	Diltiazem (N = 41)	Placebo (N = 190)
Body as a Whole					
Asthenia	9.83	22.00	22.73	12.20	7.37
Headache	11.34	22.00	13.64	7.32	14.21
Flu Syndrome	2.08	8.00	2.27	__a	1.05
Cardiovascular/Respiratory					
Palpitations	2.27	6.00	2.27	0.00	1.58
Dyspnea	3.59	4.00	5.68	4.88	2.11
Respiratory Infection	2.84	4.00	3.41	4.88	3.68
Gastrointestinal					

Dyspepsia	6.81	4.00	5.68	4.88	1.58
G.I. Distress	4.35	10.00	6.82	__a	2.11
Nausea	12.29	14.00	11.36	2.44	3.68
Dry Mouth	3.40	0.00	0.00	2.44	2.63
Anorexia	3.02	0.00	2.27	0.00	1.58
Diarrhea	7.75	2.00	9.09	2.44	2.63
Abdominal Pain	3.02	4.00	1.14	__a	3.16
Constipation	2.84	6.00	1.14	4.88	2.11
Central Nervous System					
Drowsy	3.78	4.00	4.55	__a	3.68
Insomnia	2.65	6.00	3.41	__a	1.05
Dizziness	14.74	30.00	10.23	4.88	9.47
Tremor	4.91	4.00	0.00	__a	1.05
Tremor of Hand	3.02	4.00	0.00	__a	0.53
Paresthesia	2.46	2.00	1.14	4.88	3.16
Psychiatric					
Nervous	7.37	16.00	1.14	2.44	3.68

[a] No data available.

In one twelve week controlled study, daily doses of 200, 300, and 400 mg were compared to placebo. The following table shows the rates of more common reactions (at least 5% in at least one bepridil group).

Adverse Experiences by Body System and Treatment in Greater Than 5% of Bepridil Patients in Controlled Trials

Adverse Reaction	**Bepridil HCl 200 mg (N = 43)**	**Bepridil HCl 300 mg (N = 46)**	**Bepridil HCl 400 mg (N = 44)**	**Placebo (N = 44)**
Body as a Whole				
Asthenia	13.95	6.52	11.36	2.27
Headache	6.98	8.70	13.64	15.91
Cardiovascular/Respiratory				
Palpitations	0.00	6.52	4.55	0.00
Dyspnea	2.33	8.70	0.00	2.27
Gastrointestinal				
G.I. Distress	6.98	0.00	4.55	4.55
Nausea	6.98	26.09	18.18	2.27
Anorexia	0.00	2.17	6.82	2.27
Diarrhea	0.00	10.87	6.82	0.00
Central Nervous System				
Drowsy	6.98	6.52	0.00	4.55
Dizziness	11.63	15.22	27.27	6.82
Tremor	6.98	0.00	4.55	0.00
Tremor of Hand	9.30	0.00	4.55	0.00
Psychiatric				
Nervous	11.63	8.70	11.36	0.00
Special Senses				
Tinnitus	0.00	6.52	2.27	2.27

Adverse experiences in long-term open studies were generally similar to those seen in controlled trials. Although adverse experiences were frequent (at least one being reported in 71% of patients participating in controlled clinical trials), most were well-tolerated. About 15% of patients however, discontinued bepridil treatment because of adverse experiences. In controlled clinical trials, these were principally gastrointestinal (1.0%), dizziness (1.0%) ventricular arrhythmias (1.0%) and syncope (0.6%). The major reasons for discontinuation, with comparison to control agents, are shown below.

	Most Common Events Resulting in Discontinuation		
Adverse Reaction	**Bepridil (N=515) n (%)**	**Placebo (N=288) n (%)**	**Positive Control (N=119) n (%)**

Dizziness	5 (0.97)	0 (0.0)	2 (1.68)
Gastrointestinal Symptoms	5 (0.97)	0 (0.0)	5 (4.20)
Ventricular Arrhythmia	5 (0.97)	0 (0.0)	0 (0.0)
Syncope	3 (0.58)	0 (0.0)	0 (0.0)

Across all controlled and uncontrolled trials, VASCOR was evaluated in over 800 patients with chronic angina. In addition to the adverse reactions noted above, the following were observed in 0.5 to 2.0% of the VASCOR patients or are rarer, but potentially important events seen in clinical studies or reported in post marketing experience. In most cases it is not possible to determine whether there is a causal relationship to bepridil treatment.

Body as a Whole: Fever, pain, myalgic asthenia, superinfection, flu syndrome.

Cardiovascular/Respiratory: Sinus tachycardia, sinus bradycardia, hypertension vasodilation, edema, ventricular premature contractions, ventricular tachycardia, prolonged QT interval, rhinitis, cough, pharyngitis.

Gastrointestinal: Flatulence, gastritis, appetite increase, dry mouth, constipation.

Musculoskeletal: Arthritis.

Central Nervous System: Fainting, vertigo, akathisia, drowsiness, insomnia, tremor.

Psychiatric: Depression, anxiousness, adverse behavior effect.

Skin: Rash, sweating, skin irritation.

Special Senses: Blurred vision, tinnitus, taste change.

Urogenital: Loss of libido, impotence.

Abnormal Lab Values: Abnormal liver function test, SGPT increase.

Certain cardiovascular events, such as acute myocardial infarction (about 3% of patients) , worsened heart failure (1.9%), worsened angina (4.5%), severe arrhythmia (about 2.4% VT/VF) and sudden death (1.6%) have occurred in patients receiving bepridil, but have not been included as adverse events because they appear to be, and cannot be distinguished from, manifestations of the patient's underlying cardiac disease. Such events as torsades de pointes arrhythmias, prolonged QT/QTc, bradycardia, first degree heart block, which are probably related to bepridil, are included in the tables.

OVERDOSAGE

In the event of overdosage, we recommend close observation in a cardiac care facility for a minimum of 48 hours and use of appropriate supportive measures in addition to gastric lavage. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase transmembrane calcium ion influx. Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Ventricular tachycardia should be handled by cardioversion and, if persistent, by overdrive pacing.

There has been one experience with overdosage in which a patient inadvertently took a single dose of 1600 mg of VASCOR (bepridil hydrochloride). The patient was observed for 72 hours in intensive care, but no significant adverse experiences were noted.

DOSAGE AND ADMINISTRATION

Therapy with VASCOR (bepridil hydrochloride) should be individualized according to each patient's response and the physician's clinical judgement. The usual starting dose of VASCOR is 200 mg once daily. After 10 days, dosage may be adjusted upward depending upon the patient's response (e.g., ability to perform activities of daily living, QT interval, heart rate, and frequency and severity of angina). This long interval for dosage adjustment is needed because steady-state blood levels are not achieved until 8 days of therapy. In clinical trials, most patients were maintained at a dose of VASCOR of 300 mg once daily. The maximum daily dose of VASCOR is 400 mg and the established minimum effective dose is 200 mg daily.

The starting dose for elderly patients does not differ from that for young patients. After therapeutic response is demonstrated, however, elderly patients may require more frequent monitoring.

Food does not interfere with the absorption of VASCOR. (see CLINICAL PHARMACOLOGY Pharmacokinetics and Metabolism). If nausea is experienced with VASCOR, the drug may be given at meals or at bedtime.

VASCOR has not been studied adequately in patients with impaired hepatic or renal function. It is therefore possible that dosage adjustments may be necessary in these patients.

Concomitant Use with Other Agents

The concomitant use of VASCOR and beta-blocking agents in patients without heart failure is safely tolerated. Physicians wishing to switch patients from beta-blocker therapy to VASCOR therapy may initiate VASCOR before terminating the beta blocker in the usual gradual fashion (see CLINICAL

PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED
VASCOR® (bepridil hydrochloride) tablets 200 mg (film coated light blue, scored, printed VASCOR and 200), 90 tablets (3 bottles of 30) (NDC 0045-0682-33.
VASCOR® (bepridil hydrochloride) tablets 300 mg (film coated blue, printed VASCOR and 300), 90 tablets (3 bottles of 30) (NDC 0045-0683-33.

Store at 15°-25° C (59°-77° F). Protect from light.
Printed in U.S.A.
Revised March 2000

OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
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